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Controlled release from bioerodible polymers: effect of drug type and polymer composition

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Abstract

The effect of the chemical nature of the drug on matrix degradation and drug release behavior of degradable polymers was studied, using lidocaine as a model drug in base and salt forms. We show in this study that the drug in the base form has a substantial effect on the release characteristics, through an accelerating effect on matrix degradation. Study of drug release from PdlLGA shows that lidocaine salt follows a three-phase release pattern, in contrast to the biphasic release of the lidobase. However, PLLA shows a different drug release pattern, with only a single diffusion phase exhibited for both lidobase and lidosalt. We also demonstrate that the crystallinity of matrix plays an important role on drug release profiles: a crystalline matrix (PLLA IV=2.04) releases the drug at a much slower rate compared to its amorphous counterpart of similar molecular weight (PdlLA IV=2.4). The details of the study of different factors influencing the drug release may have important implications for the control of delivery of potent drugs in various therapeutic windows.
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Keywords: Bioerodible polymer; Effect of drug; Lidocaine; Diffusion control; Degradation control; Biphasic and triphasic

1. Introduction

Drug delivery devices using biodegradable polymers use mostly diffusion for drug release. Drugs have been formulated in two basic designs: reservoirs and matrices [1–4]. Poly(lactide-co-glycolide) (PLGA) is among the few synthetic polymers approved for human clinical trials. For acidic drugs, one can expect faster hydrolysis of ester bonds because of acid catalysis. In contrast, conflicting results have been reported as to how the properties of the basic drugs contained in the matrix affect their own release. Drug release can be accelerated: basic drugs catalyze the matrix degradation and in the process accelerate their own rate of release due to a bulk erosion of the matrix [5], or drug release can be suppressed. Basic drugs can neutralize the polymer terminal carboxyl residues, so that the autocatalytic effect of acidic chain ends on polymer degradation is minimized, thereby resulting in

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a less-hydrated matrix and consequent diminished rate of the drug diffusion [6–9].

The effects of crystallinity [8,9] and composition [5,6,10] of the polymer on the matrix degradation and drug release pattern have also been reported. In the case of crystallinity, there are conflicting reports about its effect: some report an increase in rate [9,11,12], while others report a rate reduction [13].

In summary, the literature reflects contradictions about the effects of the chemical nature of the drug and of matrix crystallinity; in addition, comparison has not been made at comparable M_w and copolymer composition. We attempt in this study to report on some of the above aspects, and try to reconcile some of the reported contradictions.

Lidocaine (a Na^+ blocker and class IB antiarrhythmic) was selected as a model drug. Both the base and salt (lidocaine·hydrochloride) forms were used to study the effect of base and salt forms on the matrix degradation as well as water absorption. In vitro studies were carried out for drug release as well as matrix degradation, using buffer of pH 7.4 as the release medium. The systems have been characterized with respect to weight loss, water uptake, morphological changes, change of average molecular weight (M_w), in order to explain the kinetics of drug release and the possible pathways of matrix degradation.

2. Materials and methods

2.1. Materials

The drugs, lidocaine ($C_{14}H_{22}N_2O$, henceforth referred to as lidobase) and lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot H_2O$, HCl; henceforth referred to as lidosalt) were purchased from Sigma-Aldrich Pte. Singapore. Polylactides and the polyglycolides were purchased from Purac Far East Pte., Singapore. Table 1 summarizes details of the polymers used in this study. Molecular weights (M_w) for all the polymers in the granule and film form were determined prior to immersion, using Size Exclusion Chromatography (SEC). The numbers following the description of copolymers represent the molar ratio of monomers. Thus, PDLLGA 53/47 is a random copolymer of 53% D- and L-lactides with 47% of glycolide. For the sake of convenience, PdlLGA 53/47 0.84, PLGA 80/20 4.8, and PdlLA 2.4 would be referred to in the manuscript here onwards, as PdlLGA, PLGA, and PdlLA, respectively.

Table 1
Details of the polymers used in this study

Polymer	Intrinsic viscosity (dl/g)[a]	Average molecular weight (M_w; kDa)[b]
PdlLGA 53/47	0.84	40
PLGA 80/20	4.8	910
PdlLA	2.4	311
PLA	2.04	300
PLA	4.37	810

[a] Supplier data.
[b] Determined by SEC.

2.2. Preparation of polymer films

Polymer solutions were prepared by dissolving the materials in dichloromethane at room temperature. The solution of the drug in the same solvent was added to the polymer solution and the mixture homogenized by stirring for hours under magnetic stirring. The resulting solution was subsequently sonicated for 30 min to achieve complete homogenization. The wet film was allowed to dry under ambient conditions for 24 h, following which, the drying was continued in a vacuum oven at 30 °C, for 3 weeks. Almost complete removal of solvent is achieved under these conditions (residual solvent less than 0.3% as determined by thermogravimetry). Samples of 40×25 mm dimension and thickness 25±5 μm was cut from the dry film to be subjected to in vitro degradation and subsequent characterization.

2.3. Degradation study

All films were put into glass vials (of 60-ml capacity each) and completely submerged in 50 ml of buffer solution (pH 7.4). The individual vials with the films and buffer solution, were capped and placed in an incubator, maintained at 37±0.1 °C. Films were removed at regular intervals, rinsed with distilled water to remove deposited salts from buffer, if any, on the film surface, and characterized

with respect to water uptake and weight loss as follows:

2.3.1. Water uptake

In a typical test, the film after rinsing with distilled water was wiped, weighed, and later dried to constant weight in order to determine the weight loss. Water uptake was calculated at each time point using the following equation:

$$\%\ Water\ \ Uptake = 100 \times \frac{W_{wet} - W_0}{W_0}$$

where W_{wet} and W_0, respectively, are weights of the wet weight films measured at time t, and initial weight films before immersion. Values obtained for duplicate samples were averaged. All weights were measured to an accuracy of (±0.01 mg).

2.3.2. Weight loss

Polymer weight loss during film hydration was measured by the changes in dry weight after immersion for specified time periods. For each such test, three vials for each sample were used and the result averaged. Percent weight loss was computed according to the following equation:

$$\%\ Weight\ \ Loss = 100 \times \frac{W_0 - W_t}{W_0}$$

where W_0=initial weight; W_t=dry weight at time, t.

2.4. Thermal analysis

The DSC data were obtained from a single heating profile of the films, and thus reflect the thermal history imparted by the film preparation process. The glass transition temperature of the film samples was measured using a modulated differential scanning calorimeter, MDSC™ (DSC 2920, TA Instruments, USA). The melting point (T_m) was taken as the temperature corresponding to the maximum in the endothermic peak, and the ΔH_f was taken as the area under the same peak. An exothermic crystallization peak (T_c) soon after the glass transition step was observed with PILA films. The actual heat of fusion is the difference in the heat of fusion and the heat of crystallization, approximating the amount of crystallinity present in the material before exposure to DSC. Percent crystallinity was calculated using the equation:

$$DOC(\%) = 100 \times \frac{\Delta H_f - \Delta H_c}{\Delta H_f^0}$$

where ΔH_f is the enthalpy of fusion, ΔH_c is the enthalpy of crystallization, and ΔH_f^0 is the theoretical enthalpy of fusion of 100% crystalline sample. An enthalpy value of 93.1 J/g was used for PLA from literature [7,14].

2.5. Size exclusion chromatography (SEC)

Weight average molecular weight (M_w), number average molecular weight (M_n), and molecular weight distribution (MWD) of the polymers were determined using an Agilent series 1100 liquid chromatography system. Molecular weights of samples were obtained relative to the calibration curve using polystyrene standards (165–5000 kDa).

2.6. Scanning electron microscopy (SEM)

Surface morphology of the films was studied using SEM, for evidence of film degradation. SEM was performed on surface of the samples at different time points, for the samples from in vitro degradation. The individual dried films were gold coated (gas pressure of 20 mbar, current of 18 mA, and coating time of 75 s) and the SEM micrographs were observed at 10 kV (AS JEOL, model JSM-5410 VL).

2.7. Drug release study

Transparent, crystal-free films were obtained at drug concentrations smaller than 2% for lidosalt and lidobase. No cracks or imperfections were seen on the film surface prior to the dissolution study as indicated by scanning electron microscopy. Incorporation of drugs did not interfere with the formation of homogeneous films; the crystals were dissolved uniformly within the polymeric matrix. Films were weighed and placed inside 60-ml glass vials containing 50 ml of phosphate buffer (pH 7.4), which in turn, were tightly capped and placed inside the incubator maintained at 37±0.1 °C. Samples were removed from the vials at predetermined

intervals for quantitative estimation of the amount of drug released. In a typical test, 1 ml of the drug containing buffer solution was removed and the vial was replenished with 1 ml of fresh buffer solution, to maintain a constant volume of the release medium.

The amount of drug released was quantitatively estimated using reverse-phase chromatography on Agilent's liquid chromatography system. The HPLC method used was as follows: C-18 column (4.5×250 mm), acetonitrile as mobile phase, flow rate of 0.80 ml/min, wavelength of detector at 270 nm, and injection volume of 20 μl. The retention time for the drug (for both base and salt forms) under these conditions was 4.2 min.

3. Results and discussion

3.1. Degradation study

3.1.1. Water uptake of PdILGA and PILA, with and without drugs

Fig. 1 presents the results of water uptake for the two polymer with and without drug loading, as a function of incubation time. The water absorption profile for the drug-free polymer film without any drug is different from the profile of drug-loaded films of PdILGA. Surprisingly, percent water absorption of PdILGA with lidobase was higher as compared to the film loaded with lidosalt and the drug-free sample. It

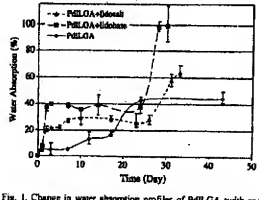

Fig. 1. Change in water absorption profiles of PdILGA (with and without drug loading) with time (days) of immersion.

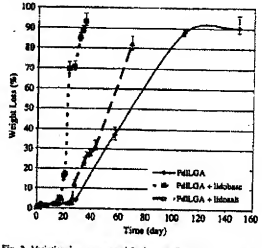

Fig. 2. Variation in percent weight loss profiles of PdILGA (with and without drug) with time (days) immersion.

was expected that the film with lidosalt would have a higher osmotic driving force for water uptake than the one with the lidobase. However, another factor appears to overwhelm the osmotic effect, as discussed below.

The second step seen in the water absorption of the drug-free PdILGA and PLGA loaded with a salt drug has been observed in an earlier study by us [15]; this is attributed to a transition from a glassy to rubbery phase.

On the other hand, PILA 4.37 (with and without drug loading) shows a different pattern (figure not shown): water absorption is very slow, with less than 4% of water uptake after 300 days of immersion, for both drug-loaded and drug-free samples. Apparently, the combination of very high molecular weight, high crystallinity and relatively hydrophobic nature of PILA matrix prevents any appreciable water uptake, within the period of investigation in this study.

3.1.2. Weight loss of PdILGA and PILA, with and without drugs

Fig. 2 presents the results of weight loss profiles (with and without drug) of PdILGA as a function of incubation time. The percent mass loss for PdILGA is characterized by an initial lag phase without appreciable detection of mass loss, followed by a sigmoid

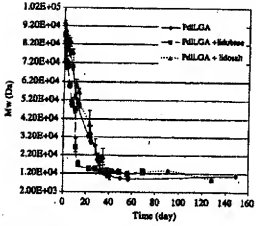

Fig. 3. Change of average molecular weight (M_w) of PdILGA (with and without drug loading) with time (days) immersion.

decay of the polymeric matrix, characteristic of a bulk degradation pattern [10,16]. In the second phase, the rate of weight loss for PdILGA loaded with lidobase is higher as compared to drug-free PdILGA or PdILGA loaded with lidosalt, characterized by a loss of substantial mass as early as day 16, well before any significant loss is seen in case of PdILGA with lidosalt (day 26) or PdILGA alone (29 days). This difference is due to the effect of base catalysis (catalytic hydrolysis of polyester linkage by lidobase) on degradation of the PdILGA.

On the other hand, very little weight loss was registered and virtually no difference was observed between the drug-loaded and drug-free samples of PILA 4.37 (figure not shown).

3.1.3. SEC analysis of PdILGA and PILA, with and without drugs

Figs. 3 and 4 present the change in weight average molecular weight of the samples of PdILGA and PILA (with and without drug loading), as function of immersion time. The fast decrease in the molecular weight for PdILGA (Fig. 3) follows an exponential pattern, representative of random chain scission in bulk degradation [10,17,18]. The matrix during this phase apparently undergoes the so-called first-order degradation. As shown in Fig. 3, the pattern of degradation of the matrix is different for drug-free and drug-loaded samples. The greater effect of lidobase in the degradation rate is clearly due to base catalysis. While most of the decrease in M_w (Fig. 3) has occurred continuously to the 23rd day for lidobase (40th day for lidosalt and drug-free

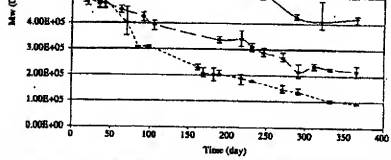

Fig. 4. Change in weight average molecular weight (M_w) of PILA 4.37 (with and without drug loading) with time immersion.

Table 2
First-order degradation constants of PdILGA: with and without drugs

First-order degradation	PdILGA	PdILGA with lidosalt	PdILGA with lidobase
Period (days)	0–40 days	0–40	0–16
k_{app} (day^{-1})	0.0184	0.0218	0.0312
R^2	0.983	0.974	0.985

PdILGA), the real threshold time for weight loss to start is 20th day (28th day for lidosalt and drug-free matrix) (Fig. 2). The samples do not show any appreciable weight loss before this threshold time because not enough leachable oligomers have been formed.

The first-order degradation constants were calculated from a linear regression analysis of the semilog plot of ln M_w vs. time as $M_w = ae^{-kt} + b$ (plot not presented). Table 2 lists the constants for the first-order degradation rate of PdILGA with and without drugs, as obtained from the slope of the straight line.

Fig. 4 shows the decrease in weight average molecular weight (M_w) of PILA matrix with and without drugs. The changes in M_w for drug-loaded samples are faster; the effect is due mostly to increased water uptake (osmotic effect).

The rate constants (k) for the first-order degradation of PILA with and without drug are obtained as above from the slope of the straight lines from the semilog plot of ln M_w vs. time. The degradation is the fastest for salt-containing film in the case of PILA (k=0.0055 day^{-1}) compared to free PILA (k=0.0019 day^{-1}) and PILA loaded with base (k=0.0028 day^{-1}), especially after day 50. This is consistent with the water absorption rates, which appear to increase for the salt-containing film after day 200.

3.1.4. Change of glass transition temperature (T_g) of the PDdILGA and PILA, with and without drug

In contrast to the T_g of PdILGA loaded with lidobese, the T_g for drug-free and lidosalt-loaded PdILGA follow the same pattern (Fig. 5). Before immersion in buffer, both drug-free and drug-loaded samples of PdILGA have T_g values higher than the average body temperature (T=37 °C). The T_g values of the drug-free and lidosalt-loaded samples of PdILGA start to decrease after about 14 days of immersion. It may be assumed that the T_g drop is due to a M_n decrease, to a value below the M_n-threshold for constancy of T_g. In contrast, T_g of PdILGA loaded with lidobase is constant for 5 days at about 39 °C followed by almost linear decrease to reach a value of ~33 °C after 30 days immersion. Hence, the drop in T_g is consistent with the significant decrease in M_n of PdILGA loaded with lidobase. From Figs. 2 and 3, we may infer that the critical molecular weight characterized by the beginning of the drop of the glass transition for this particular material might be between 40 and 50 kDa (M_w-value).

The incorporation of drug has no effect on the original T_g of the PILA. T_g (about 63 °C) is much higher than the body temperature and remains unchanged for 30 weeks.

3.1.5. Change of the degree of crystallinity of the PILA with and without drug

Interestingly, the DOC of PILA shows different patterns for drug-free and drug-loaded samples (data not shown). Drug-free PILA shows a slight increase in the degree of crystallinity over 300 days. On the other hand, samples of PILA loaded with lidosalt and lidobase show significant increase in DOC for 210 days followed by a decrease. This effect of

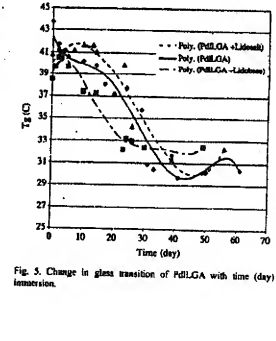

Fig. 5. Change in glass transition of PdILGA with time (day) immersion.

drug incorporation (followed by buffer immersion), increasing the crystallinity of the matrix is probably similar to the observations of increase in the crystallinity of drug-free polymer matrices upon immersion [19–22]. Initial degradation takes place in the amorphous regions, followed by depletion, which increases the overall crystallinity. The second stage of degradation takes place through a chain scission in the crystalline domains and is manifested by a decrease in the overall crystallinity of the matrix.

3.1.6. SEM analysis

The SEM micrographs of PdILGA film without any drug, PdILGA loaded with lidobase and lidosalt, before immersion into buffer, are presented in Fig. 6a–c. Micrographs of the same set of films after immersion in buffer and taken out at different time points are presented in Fig. 6d (PdILGA after 37 days of immersion), Fig. 6e (PdILGA loaded with lidobase and immersed for 30 days) and Fig. 6f (PdILGA with lidosalt immersed for 23 days).

There is appreciable erosion of the individual matrices as clear from the micrographs. The extent of erosion is more apparent in the case of drug-loaded samples and is visible in the form of pores and blisters on the sample surface. It may be noted that the micrographs of the original films (before immersion) show no evidence of drug on the surface. This is because of the lower drug loading (2% w.r.t the matrix), which is within the limit of solubility of the drug in the matrix. As discussed below, this explains the absence of the familiar burst effect.

In contrast, the micrographs of PILA film without drug, PILA with lidobase, and PILA with lidosalt, show smooth surfaces initially, and after 42 weeks of immersion into the buffer (Figures not shown).

In summary, the degradation of PdILGA samples (drug free as well as loaded with lidobase and lidosalt)

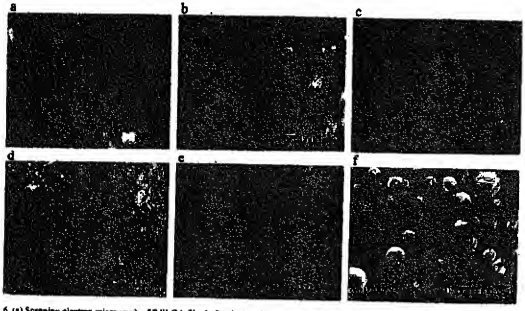

Fig. 6. (a) Scanning electron micrograph of PdILGA film before immersion into buffer. (b) Scanning electron micrograph of the lidobase-loaded PdILGA film before immersion into buffer. (c) Scanning electron micrograph of the lidosalt-loaded PdILGA film before immersion into buffer. (d) Scanning electron micrograph of PdILGA film after 37 days of immersion into buffer. (e) Scanning electron micrograph of the lidobase-loaded PdILGA film after 30 days of immersion into buffer. (f) Scanning electron micrograph of the lidosalt-loaded PdILGA film after 23 days of immersion into buffer.

is believed to be taking place through a sequence of three consecutive steps:

(1) Hydration with initial degradation characterized by a constant glass transition temperature.
(2) Further degradation occurs with a decrease of the glass transition temperature, when the M_n decreases below a certain limit.
(3) At a further degradation stage, the polymer is further cleaved to smaller molecular fragments (oligomers), which become water soluble and are then leached out.

PdILGA loaded with lidobase shows only two of the three steps in the degradation process. Because of base catalysis, stages (1) and (2) are merged, i.e., the decrease in M_n is so rapid that the T_g appears to decrease continuously.

In contrast, the degradation of PILA (with and without drugs) occurs through a very slow increase in hydration with little degradation.

3.2. Drug release study

All the drug release tests were carried out in triplicate and the results are presented as average. To our knowledge, only one report has been published of a study of the release behavior of the same drug in different forms [23]. Gallagher and Corrigan [23] found that the release of a base drug (Levamisole)

Table 3
Summary of the drug release study protocol

	Polymers	Drugs
Effect of drug	PdILGA 53:47 (IV=0.84 g/dl) (amorphous)	Lidobase and Lidosalt
	PILA (IV=4.37 g/dl) (semicrystalline)	
Effect of crystallinity	PdILA (IV=2.4 g/dl) (amorphous) (semicrystalline)	Lidobase
	PILA (IV=2.04 g/dl)	
Effect of M_w	PILA (IV=2.04 g/dl) (semicrystalline)	Lidobase
	PILA (IV=4.37 g/dl) (semicrystalline)	
Effect of composition	PLGA 80:20 (IV=4.8 g/dl) (semicrystalline)	Lidobase
	PILA (IV=4.37 g/dl) (semicrystalline)	

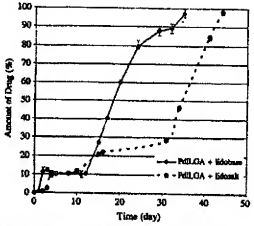

Fig. 7. Fraction of drug released from films of PdILGA 53/47 IV=0.84 vs. immersion time.

from PdILGA 50/50 (IV=0.49 g/dl) was about 7–11 times that of the salt form.

Our objective in this study was to study the effect of drug basicity, as well as of crystallinity at comparable M_w and composition, as shown in Table 3.

The drug release data obtained from the in vitro release study was analyzed for the rate of release, using the Higuchi [24] drug release equation given below:

$$\frac{M_t}{M_{inf}} = k \times t^{\frac{1}{2}} \tag{1}$$

(where M_t/M_{inf} is the fraction of drug released, t is the release time, and k is a constant characteristic of the system) or a linear relationship:

$$\frac{M_t}{M_{inf}} = k \times t \tag{2}$$

for the different stages, as explained further below.

The value of the diffusion coefficient, D, has been calculated according to the relation:

$$k = 4(D/\pi l^2)^{1/2} \tag{3}$$

where l corresponds to thickness of film or slab; which is valid for release of less than 60% of initial load, as applied to a monolithic device containing the

Table 4
Results from kinetics of drug release (lidobase and lidosalt) from PDLLGA

Effect of drug	PdlLGA with lidosalt		PdlLGA with lidobase
Period (days)	3–11	12–31	1–12
Rate k (percent day^{-1})	k_1=1.8	k_2=4.6	k_1=3.85
Diffusion coefficient (cm^2/s)	D_1=4.6 E-11	D_2=3.0 E-10	D_1=1.6 E-10
R^2	R^2_1=0.9721	R^2_2=0.9737	R^2_1=0.939

drug [24]. This equation is applied along with Eq. (1) to calculate D.

Fig. 7 shows the drug release from PdlLGA as fraction of the total loading vs. the immersion time in the release medium. It is quite clear that the drug release behavior of libase and lidosalt from the matrix are different. Release of lidobase follows a two-phase pattern. On the other hand, the salt follows a triphasic pattern. No initial burst effect was observed, apparently because of a very small drug-loading (2%). For lidobase, the first phase is diffusion-controlled release starting from day 2 to day 12. On the other hand, lidosalt follows a stage of diffusion controlled release starting from day 3 to day 11. Diffusion-controlled release from the PdlLGA matrix loaded with lidobase is faster than PdlLGA loaded with lidosalt due to higher water absorption with lidobase (Fig. 1) and (or perhaps as a consequence of the water absorption) a faster decrease of T_g (Fig. 5). At the end of day 12, the release of lidobase increases significantly: this coincides somewhat with the onset of significant weight loss, seen in Fig. 3. The release of lidobase is then linear to almost complete (near 100%) at the end of 35 days. This apparent linear rate constant can be calculated from Eq. (2), and is shown to be 3.7 day^{-1}.

In contrast, a second phase of diffusion controlled release for lidosalt takes place between 12 and 30 days. The diffusion is slightly faster in this second phase than the first (day 2–11). One explanation for this is diffusion through a swollen rubbery phase as more water is imbibed. For PdlLGA free of drug and PdlLGA loaded with salt, this starts at around day 16 (Fig. 5) roughly corresponding with the higher rate of water absorption starting at day 11 (Fig. 1). Beyond 30 days of immersion, significant release of lidosalt is registered, reaching nearly 100% at the end of 40 days. This third stage is similar to the degradation-controlled stage of the lidobase-loaded PLGA (with an apparent rate constant of 5.3 day^{-1}) and runs parallel to the weight loss phase seen around day 30 for the lidosalt (Fig. 2). The drug release path in this final stage is most likely through the water channels created by the leached-out oligomers.

As reported here, the release pattern of lidobase and lidosalt from the matrix of PdlLGA shows:

- The drug as a salt can be sustained in the matrix for longer time than its base counterpart.
- The first stage of diffusion controlled release (up to day 12) is similar for both drugs. However, the lidobase diffuses faster than lidosalt due likely to a higher water absorption rate (leading to a lower T_g matrix).
- Only the lidosalt-loaded sample shows a second diffusion phase, and it occurs between days 12–30, with a slightly faster diffusion rate. This is due to diffusion through a rubbery phase. Degradation sets in prior to the observation of this second diffusion phase for the lidobase-loaded matrix.

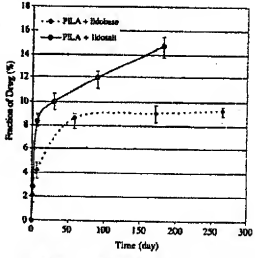

Fig. 8. Fraction of drug release from PLA IV=4.37 films vs. immersion time.

The diffusion coefficients (D) of lidobase and lidosalt from PdlLGA matrix, as obtained from plots of amount of drug release vs. square root of release time in PBS 7.4. The diffusion coefficient was not calculated for the last phase of release because that phase is degradation-controlled.

The relative magnitudes of D in the two stages (for lidosalt) are about what would be expected of diffusion through a swollen glassy and a swollen rubbery polymer (Table 4).

Fig. 8 plots the drug release from PLA 4.37 matrix, as fraction of the total loading with the immersion time in the release medium. In contrast to PdlLGA, where the base releases faster than the salt due to a higher degradation rate of the drug-loaded matrix, PlLA does not show significant level of matrix degradation. The drug release, therefore, is controlled by simple diffusion through the amorphous regions of the semicrystalline polymer and the more soluble drug (salt) diffuses faster than the hydrophobic base form.

As described above, the first-order rate constant (k) of the release process and the diffusion coefficient of the drugs from the matrix were calculated. The values of the diffusion coefficient D are, 4.29 E-14 and 6.95 E-14 $cm^2\ s^{-1}$ for PLA loaded with lidosalt and lidobase, respectively. The magnitude of the diffusion coefficient as reported here is in agreement with those reported for a medium-M_w drug from a completely glassy matrix as described by Baker [24].

Fig. 9 shows the effect of matrix composition (at comparable M_w) on release rate patterns. Lidobase release from matrices of PLA 4.37 and PLGA 80/20

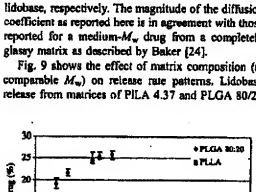

Fig. 9. Release of lidobase from PLA 4.37 and PLGA 4.8 as a function of release time: effect of composition on release.

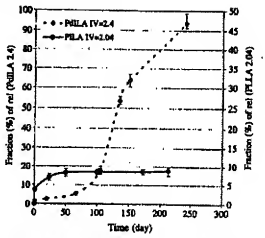

Fig. 10. Release of lidobase from PdlLA 2.4 (♦) and PLA 2.04 (●), as a function of release time: effect of matrix crystallinity on drug release behavior.

4.8 are compared. Release of lidobase from PLGA 80/20 4.8 is characterized by a diffusion phase of 80 days in contrast to 250 days for the PLA. Degradation-controlled release is not observed for either polymer in this time frame. The first-order drug release constant (k) and the diffusion coefficient (D) for the release of lidobase from PLA 4.37 and PLGA 80/20 4.8 are D=6.95 E-14 and D=3.11 E-11, respectively. It can be clearly seen that the effect of composition plays a major role on the diffusion rate of the drug through the polymer film.

In Fig. 10, we show the effect of crystallinity differences only (at comparable composition and M_w) on lidobase release rates, using matrices of PLA 2.04 and PdlLA 2.4. The results of kinetic analysis show values of D=3.84 E-14 and D=2.7 E-11, respectively, for PLA 2.04 and PdlLA 2.4. It is evident that the amorphous PdlLA has a D value that is about three orders of magnitude higher than that the crystalline PlLA. Moreover, the PdlLA matrix exhibits a two-phase release pattern for lidobase over a period of 250 days (due to degradation effects), in contrast to the single-phase behaviour for PLLA.

The glass transition temperatures of both PdlLA 2.4 and PlLA 2.04 are much higher than the test temperature of 37 °C. The amorphous phases of both the matrices are therefore in the glassy state,

so the difference in D values reflect the role of crystallinity alone (50% vs. 0%). It is interesting to note that the diffusion coefficient of the PILA 2.04 (D_1=3.84 E-14 cm^2 s^{-1}) is half of PILA 4.37 (D=6.95 E-14 cm^2 s^{-1}). This may not be surprising especially when considered in light of the fact that PILA 2.04 has distinctly higher degree of crystallinity as compared to PILA 4.37 (50% vs. 40%, respectively).

3.2.1. Comparison of lidobase release for all polymers

If we examine diffusion-controlled stages of drug release for all the polymers, in a little more detail, a definite trend emerges. Shown below are the calculated values for the diffusion coefficients, using lidobase as the diffusant:

Polymer	PILA 2.04	PILA 4.37	PdlLA	PLGA 50/20	PLGA 53/47
D	3.84 E-14	6.95 E-14	2.7 E-11	3.11 E-11	1.596 E-10
T_g* (°C)	70	62	48	50	40

* T_g values are measured for the dry polymers.

In general, the magnitude of the diffusion coefficient correlates inversely with the magnitude of measured T_g. For PILA 4.37 and PILA 2.04, which absorb very little water (the measured T_g of the dry polymer should be substantially the same as the polymer immersed in buffer), the values of D reflect diffusion through a glassy phase. For PdlLA and PLGA 80/20, which do absorb a little bit more water (and hence have T_g values lowered for the wet films), the D values represent diffusion through a swollen glassy polymer, or perhaps a rubbery polymer close to its T_g (at 37 °C). In the case of PLGA 53/47, which absorbs considerably more water, the wet polymer will have a T_g below 37 °C, and hence, the measured D is representative of diffusion through a rubbery phase.

4. Conclusions

In the literature, it is generally accepted that the rate of drug release from bioerodible polymers can be both diffusion-controlled and degradation-controlled. The drug release profile is thus generally accepted to be biphasic, showing these two mechanisms. However, when polymer and drug variables are changed, the profile deviates from the expected biphasic, due to the combined (and sometimes opposing) effects of these variables on degradation and water absorption.

In our study, we find that the effect of the chemistry of the drug on the matrix degradation dominates the release pattern, by influencing the rate of degradation as well as the rate of water absorption. Contrary to other reported work, we do not find an effect of complexation of carboxylic end groups by base, leading to slower release of the base drug. We believe that the reported complexation effects occur when dealing with low-M_w PILAs and copolymers, as the concentration of end groups is fairly high in low-M_w polymers. In our work, we demonstrate that the presence of lidobase accelerates the hydrolysis of polyester links via a base-catalyzed reaction, and that this effect dominates any other complexation effects. In addition, we believe we have shown that the main effect of the neutral form of the drug (on degradation) is through its effect on water absorption rate, due primarily to an osmotic effect. We also find the effect of crystallinity to be in contradiction to some of the earlier works, which show an enhancement of release rate with higher initial crystallinity. We find the opposite effect in all the polymers studied to date. We believe this contradiction may be reconciled by the fact that we have intentionally kept the drug concentration well below saturation limits, and some of the earlier reports of enhanced release with increased crystallinity may be attributed solely to drug de-solvation, leading to a leaching-out of drug crystals.

From the above results, we venture some generalizations regarding release patterns from PLA and PLGA polymers:

(a) Where the release is controlled solely by diffusion, higher T_g and higher crystallinity decrease release rates.
(b) The chemistry of the drug determines whether we observe a biphasic or more complex profile, in degrading systems: specifically, base drugs lead to biphasic profiles, whereas neutral drugs may promote a triphasic pattern.

(c) The molecular weight of the polymer may play a significant role in determining whether the base drug acts as a catalyst or a complexing agent.

Predictions of overall drug release profiles must take into account the basic or acidic nature of the drug, as it affects degradation, as well as osmotic effects, which determine the rate of water absorption.

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